REMARKS

Applicants request entry of the amendment and reconsideration of rejection of the claims in view of the following remarks.

Applicants have amended claim 59 to clarify the claim. Applicants submit this amendment does not raise any issues of new matter.

Applicants note that there are no outstanding rejections of claims 47-58, other than provisional double patenting rejections. Applicants presume that these claims are allowable except for that issue. Applicants request that the Examiner confirm that this is the case.

Claims 47-63 are pending in the application.

Petition for Extension of Time

It is noted that a one-month petition for extension of time is necessary to provide for the timeliness of the response. A request for such an extension is made extending the time for response from June 24, 2004 to July 24, 2004, which falls on a Saturday extending the time for response to Monday, July 26, 2004.

Rejections withdrawn

Applicants acknowledge the withdrawal of the rejection of claims 12-14, 16-18, and 34-37 under 35 U.S.C. 112, first paragraph as non-enabled. Applicants acknowledge the withdrawal of the rejection of claims 12-14, 16-18, 31, 33-45 and 47 under 35 U.S.C. 112, first paragraph as lacking written description. Applicants acknowledge the withdrawal of the rejection of claim 14 under 35 U.S.C. 112, second paragraph as indefinite. Applicants acknowledge the withdrawal of

the rejection of claims 12-14, 16-18, 34-38 under 35 U.S.C. 103(a) in view of Vaughan in view of Bosslet and further in view of Ridgway or Carter.

35 U.S.C. 103(a)

Claims 59-63 stand rejected under 35 U.S.C. 103(a) as unpatentable over Ridgway, Carter (U.S. Pat. No. 5,807,706), or Carter (WO/96/27011) in view of Kostelney and further in view of Vaughan. Applicants respectfully traverse this rejection.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) there must be a suggestion or motivation to, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, modify the reference or combine the reference teachings; and 3) there must be a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, at least because there is no motivation or suggestion to combine the references in the manner asserted by the Examiner.

As an initial matter, Applicants submit that the Carter U.S. reference (U.S. Pat. No. 5,807,706) is not prior art under 35 U.S.C. 103(c). The instant application is a continuation application of U.S. Application Ser. No. 09/070,416, filed on April 30, 1998, which claims the benefit of U.S. Application No. 60/050,661, filed on June 24, 1997, which itself claims the benefit of U.S. Application No. 60/046,816, filed March 2, 1997. The Carter reference is a U.S. patent with a filing date of May 3, 1995 and an issue date of September 15, 1998. Therefore, this references qualifies as prior art only under 102(e).

A reference that is prior art only under 102(e) cannot be used, under 103(c), in an obviousness rejection if the subject matter of the cited reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Applicants hereby make a clear statement of entitlement to exclude the Carter patent as prior art. The Carter patent is assigned to the assignee of the present application. It, and the present application were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 59-63 are directed to bispecific antibodies comprising a common variable light chain domain that has at least 98% amino acid sequence identity to a first light chain variable domain of first antibody and a second light chain variable domain of a second antibody. Applicants submit that there is no motivation to combine the cited references to obtain the present invention.

1) **The Examiner has not established a proper motivation to combine these references.**

The Examiner contends that Kostelney provides the motivation to use the method of Vaughn to look for common light chains, because Kostelney allegedly teaches that unwanted antibody product may be formed because of mismatching of light chains with heavy chains. Applicants disagree.

Applicants respectfully submit that the Examiner must consider the Kostelney reference as a whole. When the Kostelney reference is considered as a whole, one of skill in the art would not be motivated to look to other references to address the problem of mismatching of light chains.

Kostelney teach that the two proteins are mixed *in vitro* to form the bispecific antibodies, after having been expressed in separate cells. Two heterodimer-forming zipper peptides derived from the Fos and Jun proteins were respectively linked to the Fab' portions of two different mAb (145-2C11 and anti-Tac) by gene fusion (See Abstract). The anti-Tac Fab'-Jun and anti-CD3 Fab'-Fos were then expressed individually as homodimers, reduced *in vitro* to form monomers, and then mixed and reoxidized together to form bispecific antibody products (*Id.,* and page 1548, fourth full paragraph). The reference teaches that this method is preferred because of the ease of achieving purity during large-scale production of bispecific antibodies, and because "the T cell binding component of the bispecific antibody such as anti-CD3-Fos need only be generated once, since it can then be combined with a variety of Fab'-Jun components to target different cells" (page 1552, first paragraph).

Therefore, in the method of Kostelney et al., there is no opportunity for mismatching of light chains to occur. Each mAb-Fab' is individually expressed such that only the cognate light chain is available to associate with the respective Fab'. Consequently, the method of Kostelney does not have the problem of mismatched H and L chains in the final antibody product. Applicants respectfully submit that the Examiner's citations to Kostelney regarding the problem of mismatched chains relate only to a method of forming the antibody that is not the preferred method of the reference. Kostelney states that if the antibody is formed from the two Fab' proteins *in vivo* rather than *in vitro*, mismatching of H and L chains can occur (page 1551, last paragraph to page 1552, first full paragraph). Furthermore, Kostelney states that using *in vivo* methods, "it is difficult to express the two Fab' zipper proteins at equal levels in one cell line, and the excess proteins may form homodimers," implying that this method is not preferred.

Therefore, when Kostelney is considered as a whole it directs one of skill in the art away from using the *in vivo* method, where each antibody is produced in the same cell, which may lead to mispairing of H and L chains and formation of homodimers. Rather, Kostelney provide a method that eliminates the problem posed by such mismatching of chains. Furthermore, Kostelney does not teach or suggest that a method comprising selecting a common light chain be employed to address the problem of mispairing of the light chains. Consequently, one of skill in the art would not be motivated by Kostelney to seek other solutions to the problem, because Kostelney provides a solution to the problem and directs one of skill in the art away from a method where both polypeptide chains are expressed in the same cell. Therefore, Kostelney does not provide any motivation to combine the references in the manner suggested by the Examiner.

The deficiencies of Kostelney are not remedied by reference to Vaughn. The Vaughn et al. reference is directed to preparing a scFv phage library of naïve antibody variable domains. The reference describes the construction of a large repertoire of single chain Fvs derived from functional V genes. This reference describes that the same light chain was sometimes found to pair with different heavy chains. This reference nowhere discusses bispecific antibodies, nor does it suggest that identical light chains be selected for use in a bispecific antibody. The reference nowhere teaches or suggests that there is any advantage of selecting identical light chains over any other light chains.

The deficiencies of Kostelney and Vaughn are not remedied by reference to Carter (U.S. Pat. No. 5,807,706), Carter (WO/96/27011), or Ridgway. As discussed above, Carter (U.S. Pat. No. 5,807,706) is not proper prior art against the present claims. Regarding Carter (WO/96/27011), this reference is directed to engineering multimerization domains in the production of bispecific antibodies. The Ridgway reference is directed to immunoadhesins and

does not address common light chains. As the Examiner has acknowledged, both of these references "fail to teach methods of making bispecific or multispecific antibodies where each of the separate antigen binding domains shares a common light chain" (Office Action, page 4). Nor do these references provide any suggestion or motivation to use common light chains having at least 98% amino acid sequence identity to a first variable light chain domain of a first antibody and second light chain variable domain of a second antibody.

Consequently, the Examiner has not established a motivation to combine the references in a manner that teaches or suggests all limitations of the instant claims. Applicants respectfully submit, therefore, that the Examiner is exercising impermissible hindsight, by utilizing the knowledge disclosed in the Applicants' specification to provide the motivation to combine the teachings of Vaughn and Kostelney. MPEP 2145 X. A. Applicants submit that claims 59-63 are patentable over the cited references, at least for this reason and request withdrawal of the rejection.

Based on the foregoing, Applicants contend the Examiner has not established a prima facie case of obviousness for at least these reasons and request withdrawal of the 35 U.S.C. § 103 rejection.

Double Patenting

Applicants acknowledge the provisional rejection of claims 47-63 under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 30-51 of copending application no. 09/863,693. Applicants will consider filing a terminal disclaimer if appropriate to overcome this rejection.

Applicants acknowledge the provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 30-51 of copending Application No. 09/373,403. Upon notice of allowable claims in this case, Applicants will consider whether to file a Terminal Disclaimer under 37 C.F.R. 1.321(c) if appropriate to overcome this rejection.

Applicants acknowledge the provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39-49 of copending Application No. 10/143,437. Applicants request clarification of this rejection. It is Applicants belief that the pending claims in the U.S. Ser. No. 10/143,437 are claims 1-16. Upon notice of allowable claims in this case, Applicants will consider whether to file a Terminal Disclaimer under 37 C.F.R. 1.321(c) if appropriate to overcome this rejection.

Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332.5300

Date: July 26, 2004

Katherine M. Kowalchyk
Reg. No. 36,848

23552
PATENT TRADEMARK OFFICE